NTP Talks Transgenics

NIEHS and National Toxicology Program (NTP) researchers recently shared with the public their research on transgenic mouse models aimed at evaluating how they can be used for testing the carcinogenicity of chemicals and drugs. Research suggests that some of these models have the potential to identify carcinogens more quickly and at a fraction of the cost of the standard two-year rodent bioassay for carcinogenicity testing.

Promising research on three specific transgenic mouse models prompted a meeting of the NTP's Board of Scientific Counselors (BSC) at the NIEHS on 5–6 February 1998. The purpose of the meeting was to review the NTP/NIEHS efforts to evaluate these models and to discuss incorporating these models into the current chemical testing framework. The meeting, which was open to the public, was heavily attended by government and industry representatives.

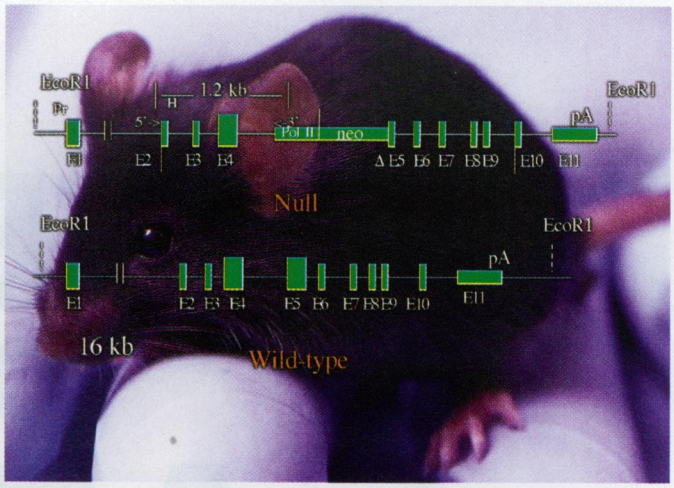
"This meeting was a milestone in the development of alternative methods," says Raymond Tennant, chief of the NIEHS Laboratory of Environmental Carcinogenesis and Mutagenesis (LECM). "It was a forum in which new data were available from NTP that could be judged for their scientific value and potential utility to the NTP."

Tennant discusses the rationale for using transgenic models, saying, "By targeting the chemical effects to genes known to play a role in tumor development, we can minimize some of the factors that complicate the bioassay results by shortening the duration of the experiment, minimizing strain- and species-specific complications and providing mechanistic insight into the action of the chemicals."

NIEHS researchers presented new findings on the p53^{def} and Tg.AC transgenic models, and researchers from Japan who have been collaborating with NIEHS scientists presented new research on the *ras*H2 model.

The p53^{def} transgenic model possesses only one functional copy of the *p53* tumor suppressor gene, which suppresses cancer in humans and rodents and is critical to the recognition and repair of DNA damage. Based on 26-week exposures, researchers have found that this model identifies transspecies mutagenic carcinogens, which are of the greatest concern for human health risks, says John French, group leader in transgenic carcinogenesis in the LECM. French presented new mechanistic data from studies with the model that showed that loss of the wild-type *p53* allele is associated with rapid induction of cancer.

The Tg.AC mouse model was produced by pronuclear injection of a v-Ha-*ras* gene, which alters signal transduction and growth control. The induction of this oncogene, which is present in all tissues of this mouse line, results in enhanced susceptibility to the development of tumors in response to physical wounding, or to mutagenic or nonmutagenic chemical carcinogens on skin and other tissues. These models have been evaluated using chemicals varying widely in their carcinogenic potency and presumed mechanism.



John French

A new breed of mouse model. The p53^{def} mouse model has only one copy of the *p53* tumor suppressor gene. The graphic overlay above compares the germline functional and inactivated *p53* alleles.

The third model presented at the meeting, the rasH2, was developed by Japanese scientists at the Central Institute of Experimental Animals in Kawasaki and the National Institute of Health Sciences in Tokyo. This model carries 56 copies of the normal human H-*ras* gene, which is involved in cell growth and differentiation. The model has been found to work well in identifying genotoxic carcinogens, says Robert Maronpot, chief of the Laboratory of Experimental Pathology at the NIEHS. Researchers have found that exposures to genotoxic carcinogens result in mutations of the normal H-*ras* gene. Studies to evaluate the model's ability to identify other types of carcinogens are ongoing, Maronpot says, and the NIEHS will continue to collaborate with Japanese researchers on this model.

Representatives from the Food and Drug Administration (FDA) and the EPA also offered their agencies' perspectives on the use of transgenic models. The FDA is "fairly open" about accepting alternative models for carcinogenicity studies on pharmaceuticals, says Joseph Contrera, associate director for regulatory research in the FDA's Office of Testing and Research. As of early 1997, the FDA will consider any scientifically justified alternative model that a sponsor may propose as an alternative to one of the two required two-year rodent assays for pharmaceuticals. "We're trying to stimulate people to develop and invest in some new approaches and supply new insight into risk assessment," Contrera says.

Speaking at the meeting, Vicki Dellarco, senior geneticist in the EPA's Office of Water, said there is a range of possibilities of how transgenic models could be utilized by the EPA, from setting research priorities to hazard ranking. Specifically, Dellarco said these shorter-term transgenic models could have an important role in testing a number of pollutants that are required to be evaluated under the Safe Drinking Water Act, possibly saving time and money.

BSC members were asked to address four questions raised by the NTP: is the NTP approach to evaluation and validation of transgenic models for use in cancer bioassays sufficient and appropriate; are the scientific needs of regulatory agencies being adequately addressed; how can existing models be best utilized (including consideration of their limitations); and what new models are needed (i.e., should the NTP seek to develop organ-specific tumor models).

A formal report from the board addressing these questions was recently submitted to the NTP, and will serve as a guide in developing future studies, says George Lucier, director of the Environmental Toxicology Program at the NIEHS. Overall, the board reacted positively to the NTP studies, saying that it is appropriate for the NTP and the NIEHS to assume a leadership role in transgenic model research, Lucier says.

The NIEHS is currently collaborating with other research groups as part of an international effort spearheaded by the International Life Sciences Institute, a nonprofit scientific organization in Washington, DC. The effort is working to test more chemicals as well as a variety of alternative models, says Maronpot. Meanwhile, he says, NIEHS and NTP researchers will continue to investigate transgenic models, looking at specific applications such as important target tissue sites in human cancer and dose–response, as well as other routes of exposure such as inhalation.

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